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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Cantor *et al.*

Serial No.: 09/880,988
Conf. No.: 5954
Cust. No.: 24961

Filed: June 13, 2001

For: *USE OF NUCLEOTIDE ANALOGS IN THE ANALYSIS OF OLIGONUCLEOTIDE MIXTURES AND IN HIGHLY MULTIPLEXED NUCLEIC ACID SEQUENCING*

Art Unit: 1634

Examiner: Chakrabarti, Arun K.

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

"Express Mail" Mailing Label Number
EV 338078507 US
Date of Deposit August 29, 2003

I hereby certify that this paper and the attached papers are being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 C.F.R. §1.10 on the date indicated above and addressed to:

Mail Stop Issue Fee
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

8/29/03 Tim J. Chettiath

TRANSMITTAL LETTER

Mail Stop Issue Fee
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith are an Issue Fee Transmittal, Comments on Statement of Reasons for Allowance, a check in the amount of $992.00 for the payment of the issue fee, publication fee and an Advance Order of 14 copies of the issued patent, and a return postcard for filing in connection with the above-identified application.

☒ The Commissioner is hereby authorized to charge any fee, including any submitted herewith if the attached check(s) is in the wrong amount or otherwise improper or missing, that may be due in connection with this and the attached papers, or with this application during its entire pendency to or to credit any overpayment to Deposit Account No. 50-1213. A duplicate of this sheet is enclosed.

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By: _____
Stephanie Seidman
Reg. No. 33,779

Attorney Dkt. No. 25491-2408
Address all correspondence to:
Stephanie Seidman, Esq.
HELLER EHRMAN WHITE & McAULIFFE LLP
4350 La Jolla Village Drive, 7th Floor
San Diego, CA 92122-1246
Telephone: (858) 450-8400
Facsimile: (858) 587-5360
EMAIL: sseidman@hewm.com

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08/29/03
Date

Tim J. Chettiath

COMMENTS ON STATEMENT OF REASONS FOR ALLOWANCE

Mail Stop Issue Fee
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313

Dear Sir:

Consideration of the following Comments on the Examiner's Statement of Reasons for Allowance are respectfully requested:

REMARKS

Any fees that may be due in connection with filing this paper may be charged to Deposit Account No. 50-1213.

Comments on Examiner's Statement of Reasons for Allowance

The Examiner alleges that the present subject matter is directed to a method for identifying nucleotides at one or more base positions in a plurality of target nucleic acid molecules, that includes:

a) synthesizing extension products of the target nucleic acid in the presence of chain terminating nucleotides and mass-matched nucleotides;

b) determining the mass of each extension product; and

c) calculating a mass shift from a period for the mass of each extension product, whereby the nucleotides in the target nucleic acid molecules are identified by determining the nucleotide that corresponds to each mass shift.

It is further alleged that Brennan (U.S. Patent 5,174,962) teaches a method that contains all of the above steps except that step a) does not include the element of "mass-matched nucleotides." The Examiner concludes that the present subject matter is novel and non-obvious because Brennan does not disclose, teach or suggest a step of synthesizing extension products of a target nucleic acid in which mass-matched nucleotides are used.

First, Applicant notes that the method having steps a) through c) as described by the Examiner and set forth above constitutes only a portion of the allowed subject matter. The instant allowed claims are directed to the following, which includes a method as described by the Examiner: (1) methods for identifying the nucleotide at one or more base positions in a target nucleic acid molecule that includes steps of synthesizing extension products in the presence of mass-matched or pair-matched nucleotides, determining the mass of each extension product and calculating a mass shift from a period for the mass of each extension product; (2) methods for detecting target nucleic acid molecules by preparing a composition of pair-matched or mass-matched nucleic acid molecules from the target nucleic acid molecules and analyzing the composition by mass spectrometry; (3) methods for detecting target nucleic acid molecules or for detecting mutations in target nucleic acid molecules that include steps of extending primers annealed to the target nucleic acid molecules in the presence of mass-matched or pair-matched nucleotides and measuring the masses and/or mass shifts of the resulting extension products; and (4) method for detecting different nucleotide base compositions in a population of nucleic acids of identical length by incorporating one or more nucleotide analogs into the nucleic acids where the nucleotide analog(s) separates the masses of nucleic acids having different base compositions in a predetermined interval.

Further, Applicant respectfully submits that none of the above methods (1) through (4) are disclosed, taught or suggested by Brennan. The Examiner recites the novelty and non-obviousness of synthesizing extension products in the presence of mass-matched nucleotides as the sole basis for allowability of the instant claims over Brennan. To the contrary, Brennan does not disclose, teach or suggest any of the instant methods (1) through (4), including various steps of the methods such as synthesizing extension products in the presence of mass-matched or pair-matched nucleotides, determining masses of extension products, calculating mass shifts of extension products, or synthesizing nucleic acids in the presence of nucleotide analogs that are used to separate nucleic acids of identical lengths but different base compositions in a predetermined interval.

Brennan is directed to a method for sequencing nucleic acids in which the terminal bases of extension products obtained by Sanger sequencing and chain termination of target nucleic acids are identified by a base-specific nuclide (*e.g.*, $^{32}S/^{33}S/^{34}S/^{36}S$ or $^{35}Cl/^{37}Cl/^{79}Br/^{81}Br$) whose combustion products (*i.e.*, SO_2, Cl_2 or Br_2) are detectable by mass spectrometry. As the Examiner has acknowledged, Brennan does not teach or suggest synthesizing extension products of target nucleic acids in the presence of mass-matched nucleotides. Applicant further wishes to point out that Brennan does not teach or suggest any method of identifying nucleotides at one or more base positions, sequencing, or detecting target nucleic acids and mutations that includes a step of synthesizing extension products in the presence of mass-matched or pair-matched nucleotides. As defined in the specification, "pair-matched nucleotides" refer to a nucleotide set in which the nucleotide analogs are selected such that the total mass of each base pair is **identical** (*see, e.g.*, page 15, line 29 through page 16, line 26 of the specification). Brennan does not disclose, teach or suggest pair-matched nucleotides, nor any methods or steps therein of synthesizing extension products in the presence of such pair-matched nucleotides.

Furthermore, Brennan does not teach or suggest measuring masses of extension products (step b) as set forth above). Contrary to the Examiner's assertion, Brennan only teaches mass spectrometric measurement of combustion products of the terminal bases of extension products, not measurement of the entire masses of extension products. In addition, contrary to the Examiner's assertion, Brennan does not teach or suggest a step of calculating a mass shift from a period for the mass of each extension product, whereby the nucleotides in the target nucleic acid molecules are identified by determining the nucleotide that corresponds to each mass shift (*i.e.*, step c) as set forth above). As disclosed in the specification, a mass shift is a deviation from a corresponding predetermined periodic reference mass, where the period is based on the mass of mass-matched or pair-matched nucleotides that are used in the step of synthesis of extension products in the instantly claimed methods (*see, e.g.*, page 18, lines 25-28 of the specification). Thus, calculation of mass shift of an extension product involves measurement of the mass of an extension product relative to a periodic reference mass, which is based on the mass of a mass-matched or pair-matched nucleotide. Since Brennan does not teach or suggest any mass-matched or pair-matched nucleotides, Brennan can not possibly teach or suggest calculation of mass shifts as set forth in step c) above.

Finally, Brennan does not disclose, teach or suggest any method of separating a population of nucleic acids of identical length and different base compositions, much less such method that includes a step of introducing nucleotide analogs into the nucleic acids where the analogs are selected to separate the population of nucleic acids according to a predetermined interval.

Therefore, Applicant respectfully submits that not only does Brennan not teach or suggest a step of synthesis of extension products in the presence of mass-matched nucleotides as acknowledged by the Examiner, Brennan also does not teach or suggest any method of identifying nucleotides at one or more base

positions, sequencing, or detecting target nucleic acids or mutations by synthesizing extension products in the presence of mass-matched or pair-matched nucleotides, determining masses of extension products and calculating mass shifts of extension products. Further, Brennan does not teach or suggest any method of separating nucleic acids of identical length and different base composition, nor any step of synthesizing nucleic acids in the presence of nucleotide analogs that are selected to separate nucleic acids of identical lengths but different base compositions in a predetermined interval.

* * *

Respectfully submitted,
HELLER, EHRMAN, WHITE & McAULIFFE LLP

By: _____
Stephanie L. Seidman
Registration No. 33,779

Attorney Docket No. 25491-2408
Address all correspondence to:
Stephanie L. Seidman
HELLER, EHRMAN, WHITE & McAULIFFE LLP
4350 La Jolla Village Drive, 7th Floor
San Diego, California 92122-1246
Telephone: (858) 450-8400
Facsimile: (858) 587-5360
EMAIL: sseidman@hewm.com